Allogeneic transplantation in acute myelogenous leukemia: a comprehensive single institution's experience

Gerard Socie,[1,2,3] Jacques-Emmanuel Galimard,[4] Emmanuel Raffoux,[1,5] Raphael Itzykson,[1,5] Pierre Edouard Debureaux,[5] David Michonneau,[1,2,3] Etienne Lengliné,[5] Marie Robin,[2] Flore Sicre de Fontbrune,[2] Marie Sébert,[6] Aliénor Xhaard,[2] Rathana Kim,[6] Anne Couprie,[6] Nathalie Dhedin,[7] Matteo Dragani,[6] Pierre Lemaire,[8] Lise Larcher,[1,8] Emmanuelle Clappier,[1,8] Nicolas Boissel,[1,7] Jean Soulier,[1,8] Hervé Dombret,[1,5] Pierre Fenaux,[1,6] Régis Peffault de Latour[1,2#] and Lionel Adès[1,6#]

[1]UFR de Médecine, Université Paris Cité; [2]APHP, Hématologie Greffe, Hôpital Saint Louis; [3]INSERM UMR 976, Hôpital Saint Louis; [4]EBMT, Statistical Unit; [5]APHP, Hématologie Adultes, Hôpital Saint Louis; [6]APHP, Hématologie Séniors, Hôpital Saint Louis; [7]APHP, Hématologie Adolescents Jeunes Adultes, Hôpital Saint Louis and [8]APHP, Laboratoire d'Hématologie, Hôpital Saint Louis, Paris, France

[#]RpdL and LA contributed equally as senior authors.

Correspondence: G. Socie
gerard.socie@aphp.fr

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Abstract

Debates on the role and timing of allogeneic hemtopoietic stem cell transplantation (HSCT) in acute myelogenous leukemia (AML) have persisted for decades. Time to transplant introduces an immortal time and current treatment algorithm mainly relies on the European LeukemiaNet disease risk classification. Previous studies are also limited to age groups, remission status and other ill-defined parameters. We studied all patients at diagnosis irrespective of age and comorbidities to estimate the cumulative incidence and potential benefit or disadvantage of HSCT in a single center. As a time-dependent covariate, HSCT improved overall survival in intermediate- and poor-risk patients (hazard ratio =0.51; *P*=0.004). In good-risk patients only eight were transplanted in first complete remission. Overall, the 4-year cumulative incidence of HSCT was only 21.9% but was higher (52.1%) for patients in the first age quartile (16-57 years old) and 26.4% in older patients (57-70 years old) (*P*<0.001). It was negligible in patients older than 70 years reflecting our own transplant policy but also barriers to transplantation (comorbidities and remission status). However, HSCT patients need to survive, be considered eligible both by the referring and the HSCT physicians and have a suitable donor to get transplantation. We, thus, comprehensively analyzed the complete decision-making and outcome of all our AML patients from diagnosis to last follow-up to decipher how patient allocation and therapy inform the value of HSCT. The role of HSCT in AML is shifting with broad access to different donors including haploidentical ones. Thus, it may (or may not) lead to increased numbers of allogeneic HSCT in AML in adults.

Introduction

Although acute myelogenous leukemia (AML) is one of the main indications for allogeneic hematopoietic stem cell transplantation (HSCT) worldwide,[1–6] its place and timing in the course of the disease remains controversial.[7–10] In the 1980's large studies compared autologous and allogeneic HSCT *versus* chemotherapy as consolidation therapies for AML in first complete remission (CR1).[11–13] Progress in disease-risk classification using cytogenetics and molecular tools allowed better risk/benefit assessment of the appropriateness of HSCT.[14] Statistical tools were also developed which addressed the survival time bias for those surviving long enough to get to transplant.[13] While earlier studies involved only younger patients (receiving myeloablative conditioning regimen) the picture of HSCT changed with the use of reduced intensity conditioning (RIC), expanded donors availability (HLA allele-matched unrelated donors [MUD] and haploidentical donors), and progressive decrease of transplant related mortality (TRM).[15–18] Similarly, novel induction, targeted and maintenance therapies plus improved supportive care have limited non-relapse mortality following non-HSCT treatments.

However, there are also inherent analytical biases in the chemotherapy-oriented literature.[7–9] Chemotherapy reports generally exclude older or unfit patients from clinical trials along with patients with therapy-related AML (tAML) (after previous chemotherapies for malignant or non-malignant diseases) or secondary AML (sAML) evolving from myelodysplastic syndrome (MDS) or myeloproliferative disorders (MPN). More recently, cytogenetic and molecular risk phenotype was used to identify patients who might not need HSCT.[19,20]

As discussed by Gale and Estey,[9] most if not all, previous studies which assessed the value of HSCT lack the denominator: i.e., how many patients with AML from an unselected population (irrespective of age, disease-type [*de novo* or sAML/tAML]), actually receive HSCT therapy? Some clinical trials or retrospective analyses claimed, especially in good-risk AML, that HSCT can safely be postponed to CR2. This second point has also been challenged (the "myth of allogeneic HSCT in CR2" due to deaths, complications or treatment failures during reinduction),[10,12] and has not been properly analyzed in an unselected AML population.

Observational studies of patients are considered important for the development of clinical trials and represent a true figure of patients actually treated.[21] Herein, we studied recent and consecutive AML patients using cytogenetic- and molecular-risk characterization to assess the cumulative incidence of HSCT and the impact of treatment choices after formal review of all patients' charts.

Methods

Four hundred and ninety-one consecutive adult (over 16 years old) patients with AML were included. All consecutive AML cases between 11, 2015 and 6, 2019 were retrospectively identified through the Leukemia Tumor Board and the diagnostic lab. Patients were diagnosed with AML according to the World Health Organization classification.[22] All had cytogenetic and molecular evaluation, as previously described.[23] Most patients were transplanted in CR1 from HLA identical siblings or matched (10/10) unrelated donors (UD), but few patients underwent HSCT from alternative donors (haploidentical or 1 antigen mismatched [MM] UD in the recent years [13/22 and 2/7 high risk patients were transplanted in CR1 from an haploidentical or a MM UD, respectively]). Additional details are provided in the *Online Supplementary Appendix*.

Outcomes

Starting from AML diagnosis, overall survival (OS) was the primary endpoint. OS was defined as time to death from any cause. Leukemia-free survival (LFS) was defined as time to first event of relapse, progression, or death. Relapse incidence (RI) was defined as time to primary induction failure or leukemia recurrence after remission; death without relapse or progression was the competing risk. Non-relapse mortality (NRM) was defined as time to death from any cause without relapse or progression; relapse and progression were competing events. Incidence of HSCT was defined as time to first allogeneic HSCT with death as competing event. Incidence of patient review (PtRv) was defined as time to PtRv with death as competing event. Incidence of CR1 was defined as time to CR1, or CRi with death and HSCT as competing events. All the outcomes were censored at last follow-up.

Additionally, outcomes were calculated from first relapse. Incidence of CR2 was defined as time to CR2 with death and HSCT as competing events. Finally, OS, LFS, RI and NRM were calculated from first allogeneic HSCT.

Statistical Analysis

Additional details are provided in the *Online Supplementary Appendix*. Multivariable analyses were performed using Cox proportional hazards models for OS and LFS, and cause-specific outcomes with competing events. Covariates included in Cox multivariable models were European LeukemiaNet (ELN) 2017, secondary AML and age at diagnosis. For OS, impact of the first allogeneic HSCT was included as a time-dependent covariate. Due to an interaction between the HSCT and the ELN2017, the impact of the HSCT on OS was evaluated separately in the good-risk and intermediate/poor-risk populations. Outcomes were presented with their 95% confidence interval (CI). Impact of covariates on outcomes were presented as hazard ratios (HR) with their 95% CI. The significance level was fixed at 0.05 and all *P* values were 2-sided. All analyses were done using R software version 4.2.0.

The overall flow and allocations of the patients with AML in the different risk categories was also analyzed in good, intermediate, and poor since timing of transplant may be different in each group. For patients with poor-risk AML, eligible patients (treatment responsive, without excluding comorbidities or acquired complications and with an eligible donor), HSCT is considered in CR1. However, patients with good risk are generally not transplanted in CR1 (even if evaluated in PtRv) and HSCT is generally delayed until CR2 (if they achieve CR2 with suitable clinical status and a suitable donor). Indication for transplant is used as consolidation therapy during CR1 for intermediate/high-risk AML but is limited by age, comorbidity, and suitable donor availability for a patient with intermediate- or high-risk AML in CR1. An HLA-identical sibling and allele HLA-matched unrelated donor was accepted in CR1 but partially matched or haploidentical alternative donors were not always considered acceptable, even if suitable in CR1.

This study has been accepted by 21-799 IRB 00003888.

Results

Median age at diagnosis was 68.9 years (range, 16.3-95), and 491 patients were included. Three hundred and eighteen had *de novo* AML (64.8%) and 173 had s/t-AML as detailed in the *Online Supplementary Table S1*. According to the ELN 2017 classification,[14] 145 (29.7%), 117 (24%), and 226 (46.3%) were classified as good, intermediate, and poor risk, respectively. Three patients (0.7% of the population could not be classified) (Table 1) (Figure 1 summarizes main the overall flow chart of the study and patient groupings in the ELN and the MRC[24] classifications, cytogenetics, and molecular characteristics). Patients' first line therapies are summarized in the *Online Supplementary Table S2*. Even though 70% had either intermediate- or poor-risk AML, only 105 patients underwent allogeneic HSCT at a median of 6.8 months from diagnosis (range, 3.3-57.3). Their median age at diagnosis was 54.2 years (range, 16.3-71.7). Donors were most often HLA-identical siblings (24.8%) or fully matched unrelated donors (MUD, 47.6%) following RIC in 69.5%. Patient, disease and transplant characteristics are shown in the *Online Supplementary Table S3*.

Clinical outcomes of the study population

With a median follow-up of 4.3 years (95% CI: 4.0-4.5), the 4-year OS of the overall cohort is 30.2% (95% CI: 26-34.5) and the 4-year cumulative incidence of HSCT 21.9% (95% CI: 18.3-25.7). Other outcomes for the overall cohort are shown in the *Online Supplementary Table S4* and include the cumulative incidence (CI) of CR1 (54.8%); 4-year LFS (21.7%); relapse-incidence (RI) (4-year RI 63.3%) and non-relapse mortality (NRM). The 1-year incidence of CR1 for the 244 patients who received first line intensive chemotherapy was 83.6% (interquartile range [IQR], 78.3-87.7).

Four-year OS by age quartiles at diagnosis ranged from 58.9% (IQR, 49.2-67.4) in patients less than 57 years to 6.9% (IQR, 2.8-13.4) for patients older than 77 years. Similarly, the 4-year CI of proceeding to HSCT dropped significantly per quartile: 52.1% (IQR, 42.3-60.99); 29.3%; (IQR, 21.5-37.5); 5.6% (IQR, 2.5-10.7) and 0%. The CI of achieving CR1 is also shown in Figure 2. The CI of HSCT declined with age as very few in the third quartile and none in the oldest group underwent HSCT. Other outcomes including the CI of CR1, HSCT, estimates of LFS, and incidence of NRM are shown in the *Online Supplementary Table S4*.

Table 1. European LeukemiaNet 2017 classification of the study population.

Variables	Modalities	Good (N=145)	Intermediate (N=117)	Poor (N=226)	Test *P*
Patient sex, N (%)	Male	74 (51)	55 (47)	129 (57.1)	0.18
	Female	71 (49)	62 (53)	97 (42.9)	-
Year of AML diagnosis	median	2017	2017	2018	0.03
	IQR	2016-2018	2016-2018	2017-2018	-
Age at AML diagnosis in years	median	64.4	68.9	70.9	<0.001
	IQR	49.8-72.9	57.3-76.1	62-79.1	-
	range	16.3-95	16.8-91.2	16.3-91.9	-
Age at AML diagnosis in years, N (%)	16-57	54 (37.2)	29 (24.8)	41 (18.1)	<0.001
	58-69	40 (27.6)	31 (26.5)	51 (22.6)	-
	70-77	32 (22.1)	31 (26.5)	64 (28.3)	-
	78-96	19 (13.1)	26 (22.2)	70 (31)	-
PtRv HSCT, N (%)	No PtRv	77 (53.1)	58 (49.6)	149 (65.9)	0.005
	PtRv	68 (46.9)	59 (50.4)	77 (34.1)	-
No PtRv reason, N (%)	Age	26 (33.8)	34 (58.6)	91 (61.1)	ND
	Comorbidities	14 (18.2)	19 (32.8)	48 (32.2)	-
	Good risk	30 (39)	0 (0)	1 (0.7)	-
	No HLA typing	7 (9.1)	5 (8.6)	9 (6)	-
Type of AML, N (%)	*de novo*	125 (86.2)	82 (70.1)	111 (49.1)	<0.001
	Secondary / transformed	20 (13.8)	35 (29.9)	115 (50.9)	-
Type of secondary AML, N (%)	MDS	14 (70)	24 (68.6)	64 (55.7)	ND
	MPN	1 (5)	4 (11.4)	23 (20)	-
	MDS/MPN	3 (15)	2 (5.7)	22 (19.1)	-
	Therapy related	2 (10)	5 (14.3)	6 (5.2)	-

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Variables	Modalities	Good (N=145)	Intermediate (N=117)	Poor (N=226)	Test *P*
Good risk characteristics, N (%)	Double *CEBPA*	12 (8.3)	-	-	ND
	inv (16)	19 (13.1)	-	-	-
	NPM1^{+}/*FLT3*-ITD^{-}	82 (56.6)	-	-	-
	NPM1^{+}/*FLT3*-ITD low	19 (13.1)	-	-	-
	t(8;21)	13 (9)	-	-	-
NPM1 FLT3-ITD ratio (8 missing), N (%)	*NPM1*$^{+}$/*FLT3*-ITD^{-}	82 (56.6)	-	-	ND
	NPM1^{+}/*FLT3*-ITD low	19 (13.1)	-	-	-
	NPM1^{+}/*FLT3*-ITD high	0 (0)	29 (25.4)	-	-
	NPM1^{+}/*FLT3*-ITD^{-} or low	44 (30.3)	85 (74.6)	212 (95.9)	-
	NPM1^{+}/*FLT3*-ITD high	0 (0)	0 (0)	9 (4.1)	-
Normal karyotype (11 missing) N (%)	No	51 (35.4)	39 (33.6)	168 (77.4)	ND
	Yes	93 (64.6)	77 (66.4)	49 (22.6)	-
Monosomal karyotype (12 missing), N (%)	No	142 (98.6)	116 (100)	154 (71.3)	ND
	Yes	2 (1.4)	0 (0)	62 (28.7)	-
Complex karyotype (12 missing), N (%)	No	136 (94.4)	115 (99.1)	131 (60.6)	ND
	> than 3 abnormalities	5 (3.5)	1 (0.9)	77 (35.6)	-
	3 abnormalities	3 (2.1)	0 (0)	8 (3.7)	-
Treatment to reach CR1, N (%)	CR1 1st line treatment	119 (82.1)	72 (61.5)	70 (31)	ND
	CR1 2nd line treatment	2 (1.4)	4 (3.4)	8 (3.5)	-
	PR1 1st line treatment	1 (0.7)	2 (1.7)	2 (0.9)	-
	PR1 2nd line treatment	0 (0)	0 (0)	2 (0.9)	-
	HSCT in active disease	0 (0)	5 (4.3)	7 (3.1)	-
	Treatment failure	12 (8.3)	21 (17.9)	109 (48.2)	-
	Treatment related mortality	11 (7.6)	13 (11.1)	28 (12.4)	-
Diagnosis to CR1 (months)	median	1.6	1.6	1.9	ND
	IQR	1.4-1.8	1.5-2.3	1.6-3.9	-

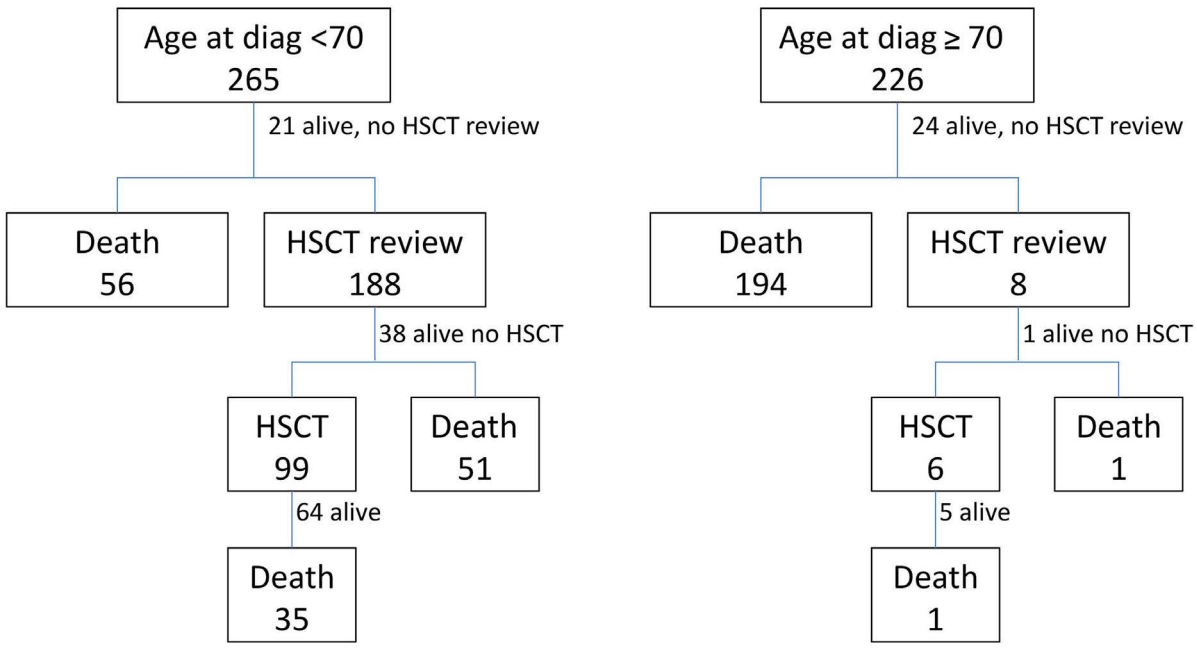
Three patients cannot be classified according to European LeukemiaNet 2017. AML: acute myeloid leukemia; PtRv: patient review meeting; IQR: interquartile range; ITD: internal tandem duplication; ND: not determined; HSCT: hematopoietic stem cell transplantation; CR1: 1st complete remission; PR1: 1st partial remission; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm.

ELN2017 good risk had, 4-year OS of 48.7 (IQR; 39.9-56.9); intermediate risk 40 (IQR, 30.7-49.2); and poor risk 13.6 (IQR, 9.3-18.7). The 4-year CI of HSCT for good risk was 19.5 (IQR, 13.3-26.6); intermediate risk 34 (IQR, 25.4-42.8) and poor risk 17.5 (IQR, 12.8-22.7). The CI of CR1 and that of HSCT are illustrated in Figure 2. From Figure 2E it can easily be seen that CI of HSCT logically varied with age and none of the patients in the older quartile (77-96 years) and very few in the third quartile (range, 69-77) underwent HSCT.

We then performed two different multivariable analyses (see statistical section) to assess OS. In good-risk AML, older age (HR=1.33; range, 1.20-1.48 per 5 years; *P*<0.001), secondary AML (HR=1.84; range, 1.03-3.30; *P*=0.04) and allogeneic HSCT (HR=2.42; range, 1.08-5.45; *P*=0.03) were each independently associated with poorer survival (Table 2A). However, in intermediate- and poor-risk AML, multivariable analysis showed that older age (HR=1.15; range, 1.09-1.22; *P*<0.001) and poor *versus* intermediate risk (HR=1.98; range, 1.49-2.62; *P*=<0.001) were independently associated with poorer survival. OS of *de novo* and secondary AML were similar (HR=1.01; range, 0.78-1.29; *P*=0.96). Allogeneic HSCT in the intermediate- and high-risk category was associated with better OS (HR=0.51; range, 0.32-0.80; *P*=0.004) (Table 2B).

Restricted to analysis of patients younger than 70 years at diagnosis, the CI of CR1, CI of HSCT, NRM, RI as well as OS and LFS were close to those of the overall population (*Online Supplementary Figure S1*). As expected, the overall CR1 rate was higher 72.1 (IQR, 66.2-77.1), as well as the rate of HSCT 38.2 (IQR, 32.2-44.2), overall. For patients in the first age quartile (range, 16-57) the rate of HSCT was 52.1 (IQR, 42.3-60.9) as compared to 26.4 (IQR, 19.4-34) in patients older than 57 (26.4; IQR,19.4-34; *P*<0.001). However, when studying the qualitative interaction of HSCT effect with ELN2017 groups, results were unchanged. When HSCT was considered as a time-dependent covariate HSCT was associated with borderline decreased survival rate in good-risk patients (HR=2.34; IQR, 0.99-5.51; *P*=0.052) but increased survival in intermediate/high-risk patients (HR=0.52; IQR, 0.31-0.87; *P*=0.01).

Although limited by patient or transplant numbers (especially in good-risk patients), the corresponding feature for LFS for patients transplanted in CR1 was: 0.53 (range, 0.16-1.77) in good-risk patients (8/121; *P*=0.3), 0.24 (range,



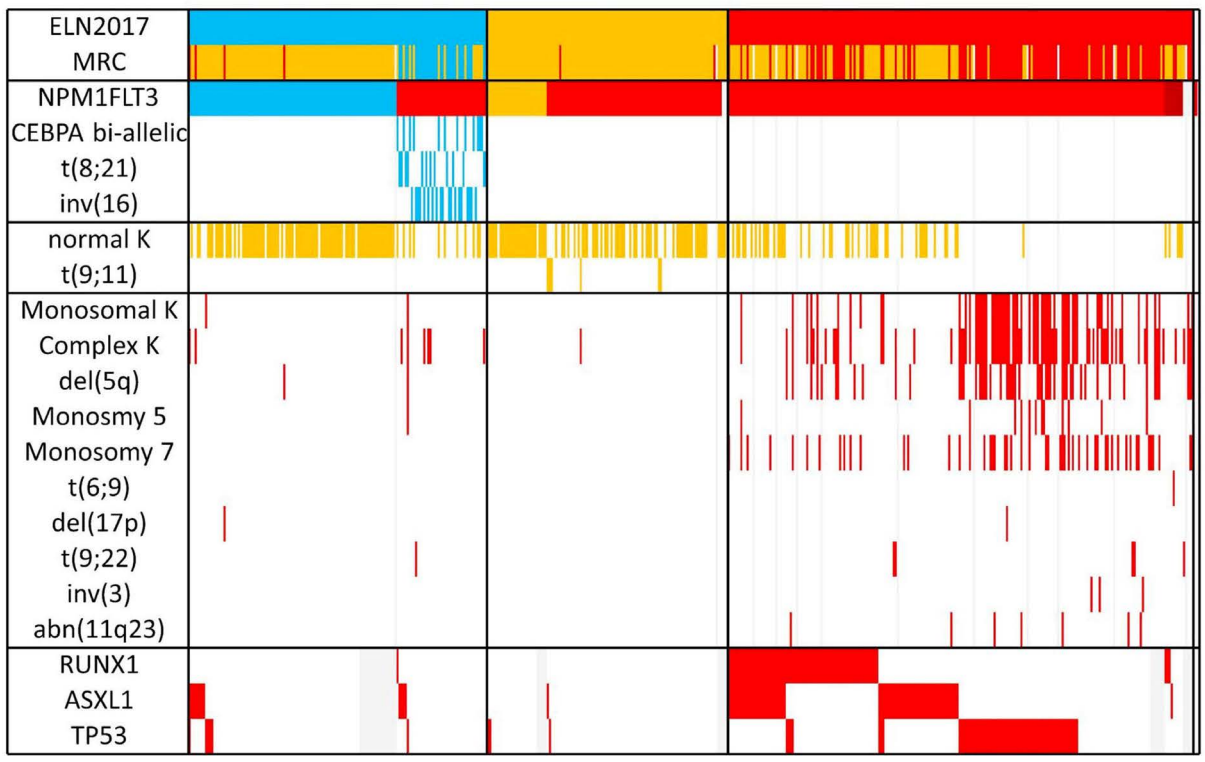


Figure 1. Flow chart and main disease characteristics. (A) Flow chart of the study. (B) Molecular and cytogenetic subtypes of acute myeloid leukemia (AML). Color legend: European LeukemiaNet 2017; good risk in blue; intermediate risk in orange; high risk in red. *NPM1*$^{+}$*/FLT3*$^{-}$ or low in blue; *NPM1*$^{+}$*/FLT3* high in orange. *NPM1*$^{-}$*/FLT3* high in dark red. K: karyotype. HSCT: hematopoietic stem cell transplantation, diag: diagnosis.

0.08-0.72) in intermediate-risk (24/76; *P*=0.01), and 0.54 (range, 0.25-1.15) in poor-risk (N=28/78; *P*=0.11).

After relapse the 1-year incidence of CR2 was 32.3% (range, 24.6-40.2) being 47% (range, 34.8-85.2), 28.6% (range, 13.7-45.4) and 7.9% (range, 2-19.3) for good, intermediate, and poor risk, respectively. One year incidence of HSCT was 23.4% (IQR, 14-34), 30.4% (IQR, 14.5-48) and 7.9% (IQR, 1.9-19.5) for good-, intermediate-, and poor-risk AML, respectively. Most importantly, 1 year OS was 39.2 (IQR, 31-47.3) for all patients, and 48.4 (IQR, 36.2-59.6), 31.3 (IQR, 15.8-48.1) and 28.5 (IQR, 15.2-43.3) for good, intermediate, and poor risk, respectively.

Outcomes after HSCT (irrespective of disease status before transplantation) are summarized in the *Online Supplementary Figures S2* and *S3* and *Online Supplementary Table S5*. OS was not statistically different with differing donor types, ELN classification, *de novo versus* sAML or tAML, but in univariate analyses, both younger age at HSCT and myeloablative conditioning were associated with significantly better outcome. Other endpoints including 2-year LFS, RI and NRM are summarized in *Online Supplementary Figures S2* and *S3* and *Online Supplementary Table S5*.

Outcome for those receiving patient review

However, success in proceeding to HSCT does not fully reflect the overall process of evaluation for HSCT. Transplant patients need to survive, be considered eligible by the referring physician (based on age, comorbidities, and disease risk), have an available donor, and be accepted by the transplant physicians. These parameters are included in the time dependent cumulative incidence of PtRv. All AML cases are discussed in our institutional PtRv, but only selected cases are discussed in the transplant PtRv. As shown in Figure 3, the CI the incidence of PtRv was slightly but not significantly different from the CI of HSCT. The 100-day CI of transplant PtRv was 36.1 (IQR, 31.8-40.5) but statistically varied according to age (*P*<0.001). Similarly, PtRv was less frequent in ELN poor prognosis AML. The 100-day

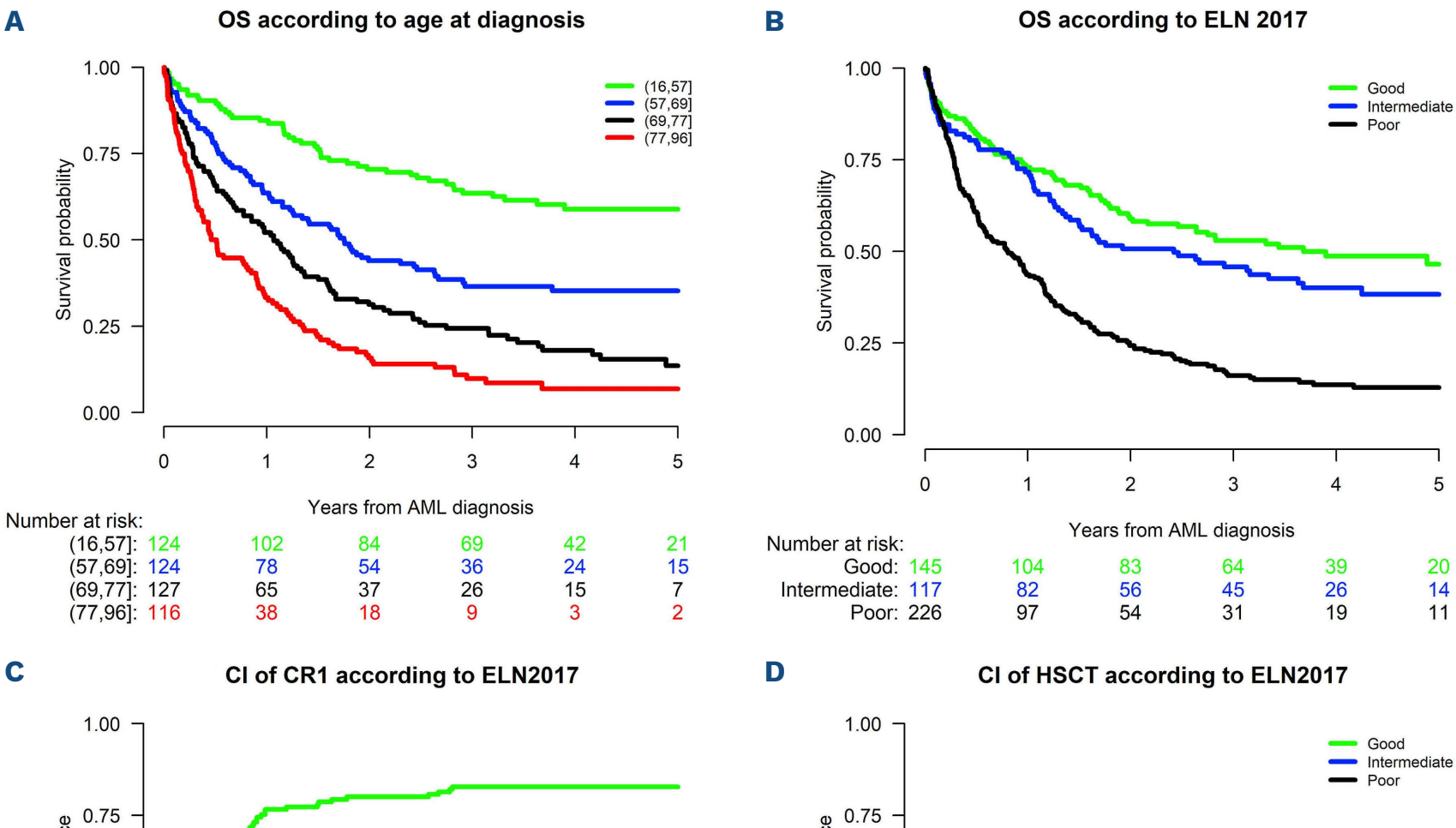


Figure 2. Outcomes from diagnosis. (A) Overall survival (OS) according to age at diagnosis (per quartile); age <57; 58-69; 70-77; and >77; (B) OS according to European LeukemiaNet (ELN) 2017; (C) cumulative incidence (CI) of first complete remission (CR1); (D) CI of hematopoietic stem cell transplantation (HSCT); (E) CI of HSCT according to age (per quartile); (F) overall CI of HSCT.

CI of PtRv for *de novo* AML was 43.1 (IQR, 37.6-48.5), but only 21.9% (IQR, 15.7-28.7 for secondary AML; *P*<0.001) (Figure 3A, D). Overall, 77 (53.1%), 53 (48.2%) and 144 (65.5%) of good-, intermediate-, and poor-prognosis AML were never discussed in the PtRv for HSCT.

Among all these 287 patients who were never discussed, main factors associated with their exclusion were older age (n=152, 53%, median age at diagnosis of 79 years; range, 65-95) and comorbidities (n=83, 29%). Intensive induction chemotherapy *versus* HMA-based treatment were delivered in 20% and 55% of those discussed or those excluded from PtRv. Additionally, even after excluding age and comorbidities 31 patients (10.8%) of good-risk patients were also excluded from PtRv.

Among 204 patients who were considered at HSCT PtRv, still 99 (48.5%) did not received HSCT (median age 53 years; range, 18-72); 76 of 99 received intensive induction and 22 of 99 were good-risk AML. Among the 22 good-risk patients, all reached CR1 yet three had no donor (*Online Supplementary Table S6*). Among all patients with PtRv for transplant: 40 (19.9%) survived at last follow-up without HSCT, 59 (29%) died without HSCT and 105 (52.2%) underwent transplantation. After PtRv, the decision was to not proceed with transplantation in 36 patients (1 due to age, 13 due to comorbidities, 22 being good-risk). For the remaining 62 patients who were considered for HSCT but were not transplanted the flow chart is provided in in *Online Supplementary Figure S4*.

Flowcharts of all acute myeloid leukemia patients' disposition; divided by European LeukemiaNet risk

The flowchart of good-risk AML is displayed in the *Online Supplementary Figure S5*. Patients with good-risk AML (n=145) had a median age of 64.4 years (range, 16.3-95) and 114 (78.5%) received intensive induction chemotherapy (Table 1; *Online Supplementary Table S2*). The 1-year CI of CR1 was 82.8% (IQR, 75.4-88.1); 4-year CI of HSCT was 19.5%, and 4-year OS was 48.7% (Figure 2). Only few transplants were performed in the first year post diagnosis (Figure 2). After achieving CR1, 72 relapsed and of these 35 (49%) reached CR2 (1-year CI of CR2; 47%; IQR, 34.8-58.2) and only 15 of 35 (43%) received allogeneic HSCT in CR2 (only 20.8% of all who relapsed); 1-year CI of HSCT 23.4 (IQR, 14-34). Of note, among the 31 patients who died post relapse, 24 were never reviewed for transplantation mostly due to their age and comorbidities (n=16, 66.7%). Donor availability and exclusions from PtRv are shown in the *Online Supplementary Figure S5*.

Intermediate-risk AML (n=117) patients are shown in the *Online Supplementary Figure S6.* They had a median age of 68.9 years (IQR, 57.3-76.1) and 71 (60.7%) received intensive induction chemotherapy (Table 1; *Online Supplementary Table 2S*). The 1-year CI of CR1 was 61.5% (IQR, 52-69.79), the 4-year CI of HSCT 34% (IQR, 25.4-42.8), and the 4-year OS was 40% (IQR, 30.7-49.2) (Figure 2). From the 117 intermediate-risk patients, 76 reached CR1. Their median age was 66 years (range, 17-86) and 59 (78%) had received in-

Table 2. Multivariate analyses on overall survival: (A) European LeukemiaNet good risk, (B) European LeukemiaNet intermediate and poor risk.

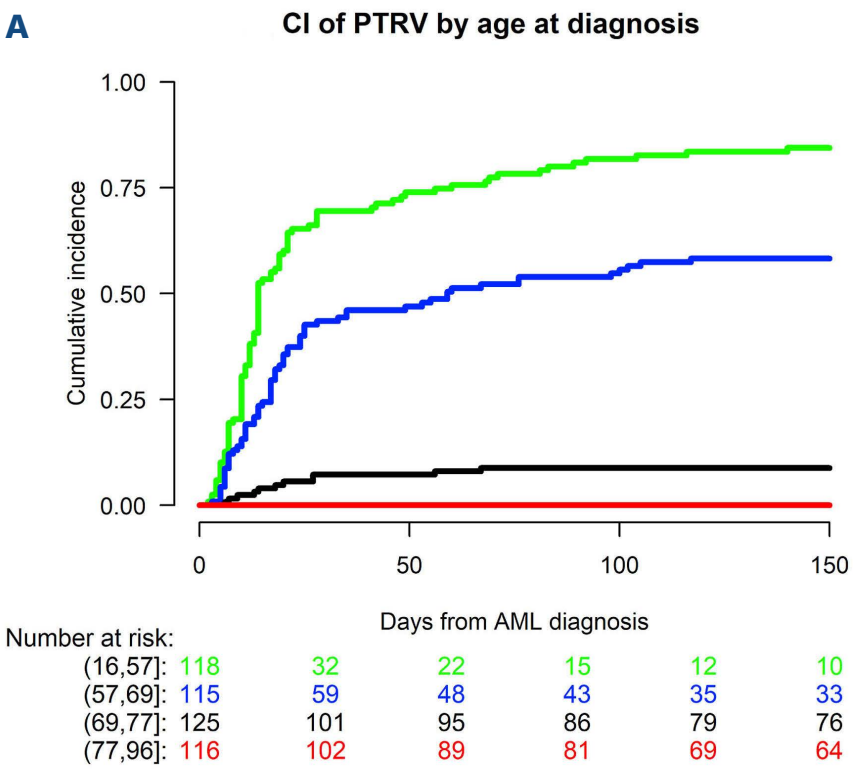
A

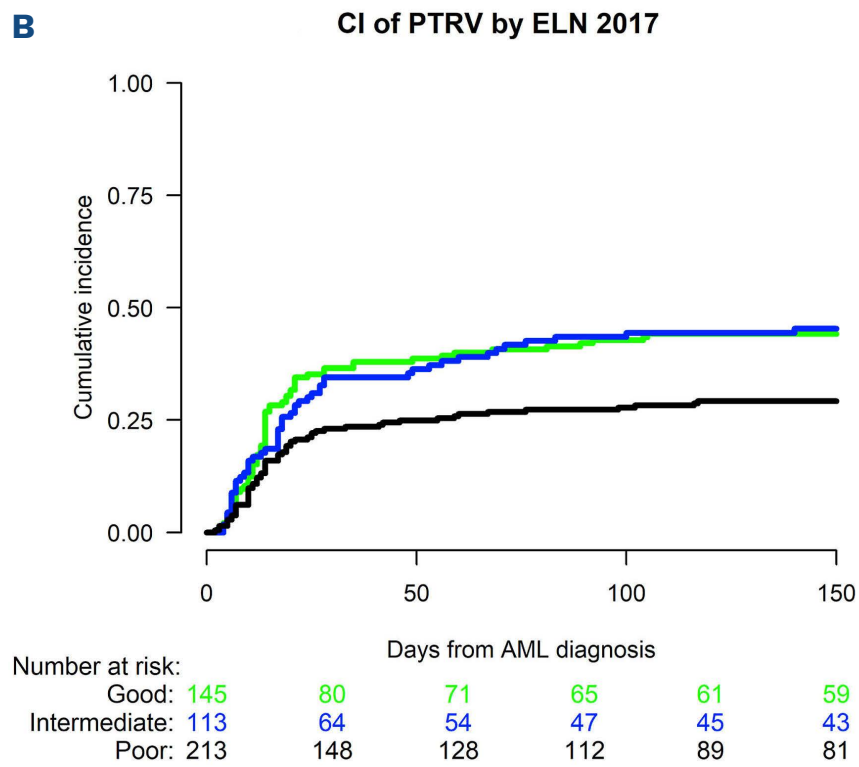
Variables	Modalities	OS	
		HR (95% CI)	*P*
Type of AML	*de novo*	1	-
	Secondary	1.84 (1.03-3.30)	0.04
HSCT	No	1	-
	Yes	2.42 (1.08-5.45)	0.03
Age at AML diagnosis (by 5 years)		1.33 (1.20-1.48)	<0.001

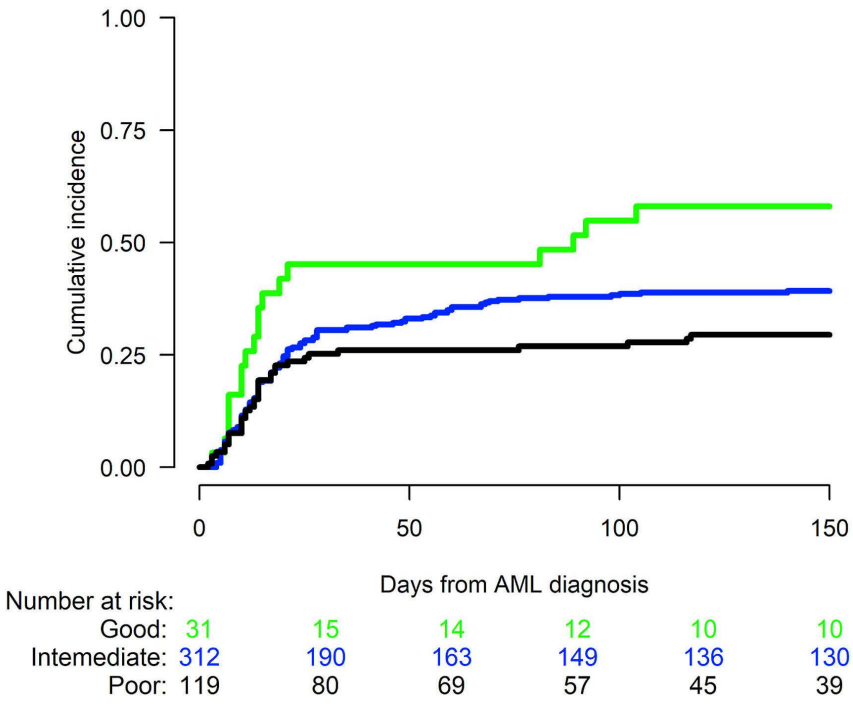
B

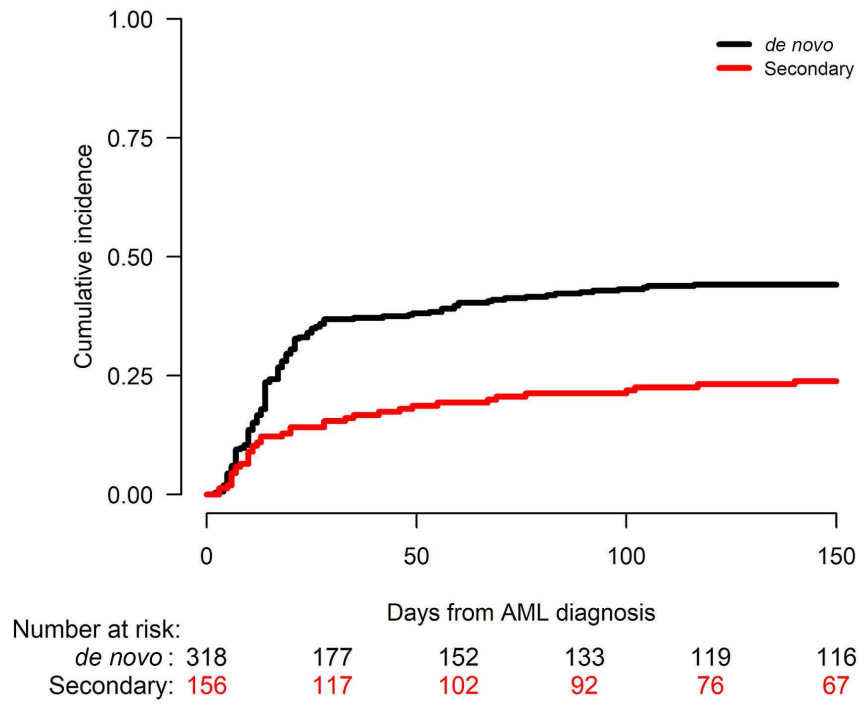
Variables	Modalities	OS	
		HR (95% CI)	*P*
ELN2017	Intermediate	1	-
	Poor	1.98 (1.49-2.62)	<0.001
Type of AML	*de novo*	1	-
	Secondary	1.01 (0.78-1.29)	0.96
HSCT	No	1	-
	Yes	0.51 (0.32-0.80)	0.004
Age at AML diagnosis (by 5 years)		1.15 (1.09-1.22)	<0.001

OS: overall survival; AML: acute myeloid leukemia; HSCT: hematopoietic stem cell transplantation; HR: hazard ratio; CI: confidence interval; ELN: European LeukemiaNet.









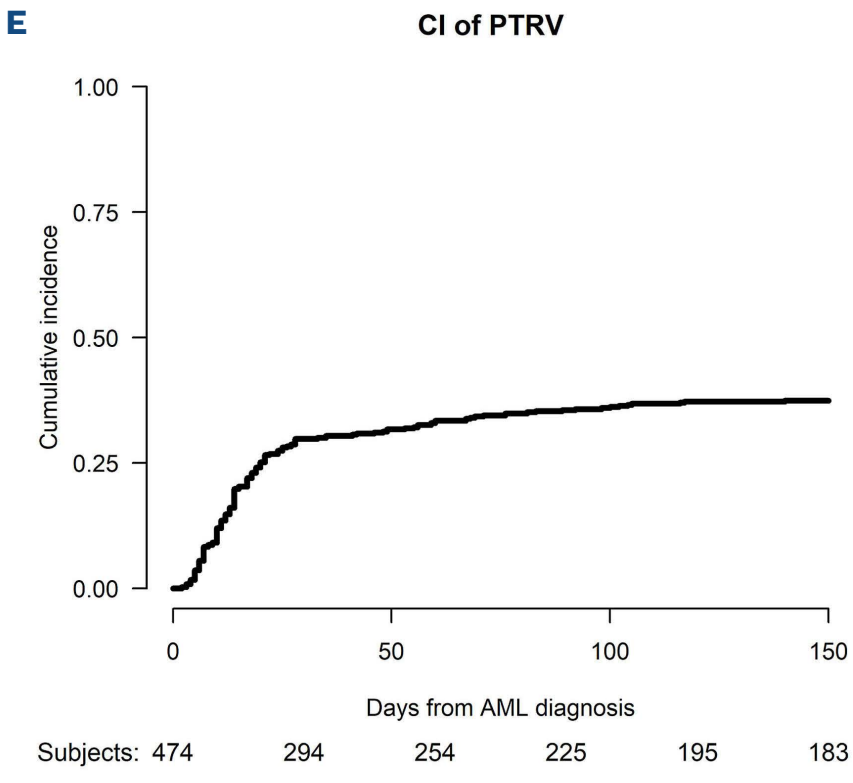


Figure 3. Hematopoietic stem cell transplantation candidate patient review by clinical characteristics. (A) Cumulative incidence (CI) of transplant candidate patient review (PtRv) by age quartile. Consideration of transplant was significantly lower in older patients (100-day cumulative incidence [CI] of PtRv was 81.8 (interquartile range [IQR], 73.3-87.7), 55.7 (IQR, 46-64.2), 8.8 (IQR, 4.7-14.7) and 0%. (B) CI of transplant PtRv by European LeukemiaNet (ELN) 2017. 100-day CI of PtRv: 42.8 (IQR, 34.6-50.7), 44.4 (IQR, 35-53.4) and 27.8 (IQR, 21.9-33.9) for good, intermediate, and poor risk, respectively; $P<0.001$. (C) CI of transplant PtRv by according to the Medical Research Council (MRC) classification. (D) CI of transplant ground round (PtRv) according to *de novo vs.* secondary acute myloid leukemia. (E) Overall CI of PtRv. AML: acute myeloid leukemia.

tensive chemotherapy. After reaching CR1, 33 patients relapsed (median age was 71 years (range, 37-83) and 24 (73%) had received intensive chemotherapy. Among these 33 relapsing patients, ten (30%) reached CR2 (1-year CI of CR2; 28.6%, IQR, 13.7-45.4) while only seven of ten (70%) received allogeneic HSCT in CR2. Most of them were not considered for HSCT because of age and/or comorbidities. Their donor availability and other exclusions criteria are shown in the *Online Supplementary Figure S6*.

Poor-risk AML patients (n=226) are shown in the *Online Supplementary Figure S7*. They had a median age of 71 years (range, 16-92) and 59 (26%) received intensive induction chemotherapy (Table 1; *Online Supplementary Table S2*). Their 1-year CI of CR1 was 34% (IQR, 27.8-40.2), 4-year CI of HSCT was only 17.5% (IQR, 12.8-22.7), and 4-year OS was 13.6% (IQR, 9.3-18.7) (Figure 2). Of these 226 poor-risk patients, 78 (35%) reached CR1. Their median age was 65 (range, 16-89) and 39 (50%) had received intensive chemotherapy. Yet after reaching CR1 (28; 36%), 35 relapsed (median age was 70; range, 16-84) and 17 (49%) had received intensive chemotherapy. Among these 35 relapsing patients, three (8.6%) reached CR2 (1-year CI of CR2; 7.9%; IQR, 2-19.3) and only one patient then received allogeneic HSCT in CR2 (3% of those who relapsed). Among the 29 patients who died post relapse, 17 did not have PtRv because of age and comorbidities.

Discussion

Four decades of debate considered the role of allogeneic HSCT as post remission treatment of AML.[2,3,18,25,26] Most analyses did not consider how many patients achieved remission but did not proceed to a transplant whether due to patient or disease characteristics, suitable donor availability or from physicians' or patients' choice. In the present study we included all recent adult patients fully characterized at the clinical, cytogenetic, molecular, and therapeutic levels. The main endpoint was OS. The main factors affecting OS were older age and ELN disease risk.[2,3,25,27,28] The patient and disease characteristics were as expected[29] and their management of patients met recent standards of care.[27]

We first assessed concordance of our findings with recent evidence-based reviews and recommendations.[3,25] Indeed, considering HSCT as a time-dependent covariate and age, patients with intermediate- and poor-risk AML had improved survival with HSCT while patients with good-risk did not. Overall, the 4-year CI of HSCT in the whole population was 22%. Only one review by Appelbaum provided a crude estimate of HSCT of 25% comparing transplants reported to the CIBMTR *versus* the expected incidence of AML by SEER in 2015.[18] In a prior cohort from the Fred Hutchinson Cancer Research Center 78 of 287 patients with newly diagnosed AML (median age 57 years) received a transplant in CR1[30] and another study at the MD Anderson testing RIC HSCT in older patients with AML or MDS, reported that only 14 of 259 (5%) patients were transplanted.[31] In a national, population-based cohort, Ostgard reported that 19% of all patients (crude estimate) underwent HSCT for AML while in CR1.[32] Finally, one recent study reported a CI of HSCT with competing risk in a propensity score-matched design evaluating the value of venetoclax in patients with newly diagnosed AML.[33]

Increasing numbers of studies report the outcome of older patients who underwent allogeneic HSCT in AML (reviewed in[34] and[16–18,35,36]). Yet, how many older patients are transplanted is unknown. These papers only report the feasibility of HSCT in selected older patients. In our inclusive cohort, the CI of HSCT varied with age with none of the patients in the oldest quartile and very few in the third quartile who underwent HSCT. Restricting the analyses to patients aged <70 years demonstrated only slightly different results from the overall population with similar trends in HSCT use and outcomes. Although the current study reflects only our own practice and, thus, there is bias of physicians being pro or con in discussing HSCT in older patients, it is likely that the number of such transplants will increase in our team but will be limited to a minority of patients fit enough to undergo HSCT (based more on physiological well-being than on calendar age).

A recent prospective study by the NRCI (AML 16 protocol) studied the value of RIC HSCT in patients aged 60-70 years.[16] Only 15.4% of the patients underwent HSCT and patients selected for transplantation were more likely to be <65 years old and have a better performance score. The 4-year CI of HSCT also varied according to the ELN classification with 27.9% in good-risk; 58% intermediate- and 37% in poor-risk leukemia. This possibly reflects hesitance to use HSCT in good-risk patients and treatment failures preventing HSCT in the poor-risk group. Here again, current data reports the outcome of transplanted patients according to the ELN classification[28] or provide recommendations for HSCT according to ELN.[3] In our good-risk ELN patients all but eight patients with high-risk feature were transplanted in CR2 (or beyond) but data reported herein, not only show that the shape of the CI curve varied according to ELN (reflecting transplant in CR1 *vs.* beyond CR1) but also provide new results showing notably that at 4 years the CI of HSCT in patients with good-risk AML reach that of poor-risk. Most recently Sorror *et al.* evaluated the benefits of allogeneic HSCT in older (or comorbid) patients with AML and provided no evidence for a benefit of allogeneic HSCT after adjustment for geriatric evaluation. Of note, only 77% of the patients had newly diagnosed AML in this cohort.[37] Altogether, our own results and current literature point out the fact that although HSCT is "feasible" in elderly patients it can only be performed in a minority of fit pa-

tients in remission.

Variation in the CI of HSCT according to ELN led to the questions: how many patients in each category were considered for transplantation; and what is the eventual allocation of patients from diagnosis until transplant, no transplant, or death? More than half of the patients were not considered for HSCT. Older age and / or comorbidities in 80% of these patients precluded HSCT consideration. Yet another 20% of patients were not discussed mainly because they had good-risk leukemia. Of 201 patients considered for HSCT, 37 (18%) did not receive HSCT as most of them (65%) had good-risk AML. Finally, we analyzed the allocation of all patients in the three ELN categories from diagnosis. In good-risk patients (n=145), 72 relapsed. The 1-year CI of CR2 was 47.0% and only one in four underwent transplantation. However, since only 35 relapsed good-risk patients achieved CR2 and of those only 15 of 35 (20.8% of those who relapsed) received an allograft in CR2, this may misrepresent the utility of HCT for good-risk AML since few could actually receive it. While the NRCI in 2013[12] suggested a rationale to postpone transplantation to CR2 because good-risk patients could be salvaged by transplant in CR2 - yet only a net 12-15% of relapsed patients went on to allografting.

Molecular monitoring of measurable residual disease (MRD) in CBF, CEBPα, and NPM1-mutated good-risk leukemias[38-36] or with multicolor flow cytometry may recognize an increasing level of MRD. Earlier re-induction may possibly improve the rate of CR2 yet needs to be demonstrated. For intermediate risk the CI of CR2 was 28.6% and only seven of ten finally underwent allogeneic HSCT. For poor risk, the 1-year CI of CR2 was low (7.9%). Altogether, these data for intermediate- and poor-risk patients, reinforce the indication for transplantation in CR1 (reviewed in[3,34]), whatever the donor type is.

While this study provides comprehensive estimates on the CI of transplantation and a detailed description of outcomes, it has some limitations. Our overall approach in the transplantation decision only reflects that of the Hospital Saint Louis in the given period. Other centers are prone to perform HSCT in older patients or to use alternative donors more frequently than we do. Confirming these findings in a larger multi-institutional cohort would help to verify our conclusions. Modern advances in molecular sub setting, ongoing improvements in supportive care and targeted post HSCT therapy may yield continuing advances. The ultimate goal is to better identify patients who most likely benefit from early HSCT and need intensified and more effective anti-leukemia measures in order to cure more patients.

Disclosures

No conflicts of interest to disclose.

Contributions

GS, ER and LA designed the study. JEG performed all statistical analyses. GS, JEG, and LA wrote the manuscript. All authors reviewed and approved the final version.

Acknowledgments

This article is dedicated to our friend Elihu Estey who sadly died during the collection and analyses of our data. His deep understanding of AML and his major impact in dissecting biases in the literature on the treatment of AML served as a major driver in the design of this study.

Data-sharing statement

This is a not an intervention study and there is no data-sharing plan for this study since the requirements by the International Committee of Medical Journal Editors are not applicable for this study. Individual participant data will not be shared. However, reasonable requests for data-sharing can be addressed to GS.

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